OC39 - Cognitive Improvement in Mild to Moderate Alzheimer's Patients: Final Results of an Open Label, Phase 2A Study of T3D-959

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Clinical Trial Sites

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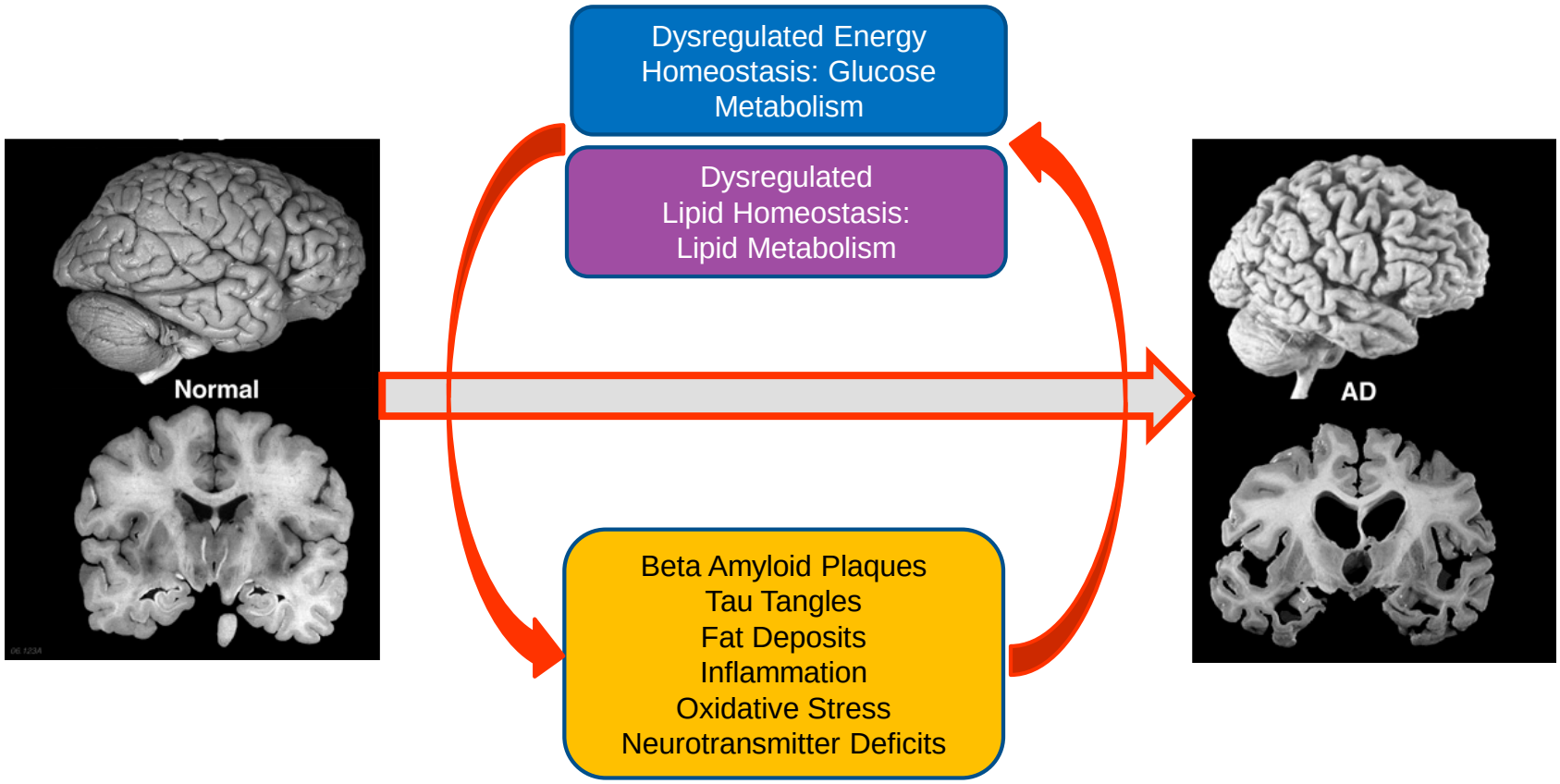
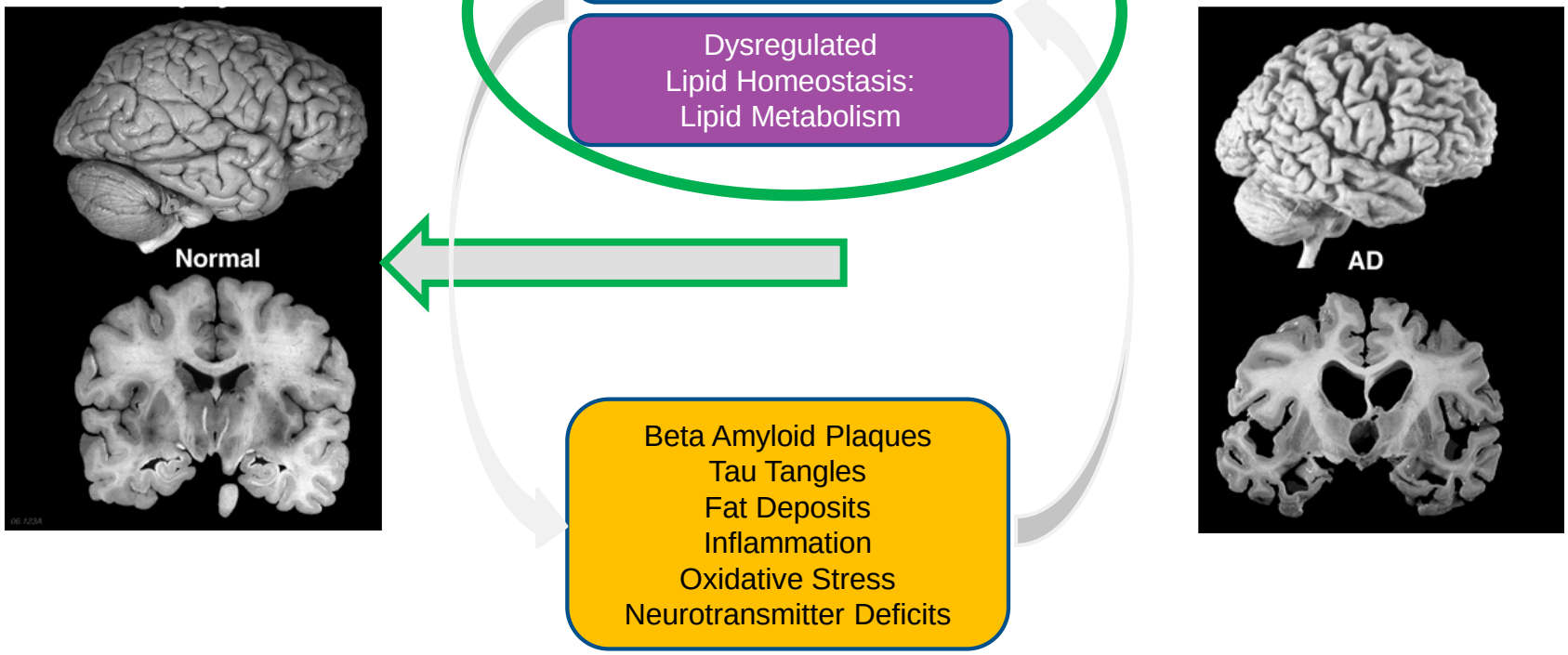
- Miami Jewish Hospitals, Miami, FL. Dr. M. Agronin
- Brain Matters Research, Delray Beach, FL. Dr. Mark Brody

Novel Approach: The Metabolic Hypothesis of AD



Massive Positive Feedback Loop Driving Neurodegeneration

Scientific Rationale: T3D-959 Breaking the Cycle – Disease Modification Potential

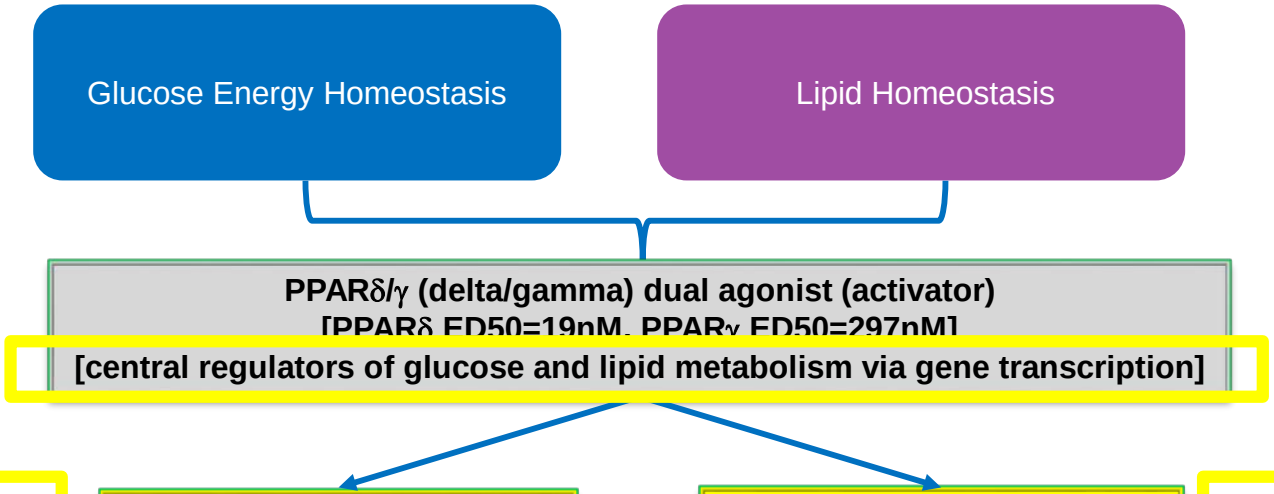


Massive Positive Feedback Loop Driving Neurodegeneration

Novel Approach: The Metabolic Hypothesis of AD

- **Massive positive feedback loop of altered glucose/lipid metabolism alterations and pathological sequelae**
- **Metabolism function alterations (glucose and lipid) antedate structural change**
- **Decreased glucose metabolism inherent in neurodegeneration**
- **Aberrant lipid metabolism is a 3rd pathological hallmark of AD**
- **Intertwined molecular interactions – Abeta and Insulin**
- **Similarities of brain and peripheral insulin resistant diseases: AD and Type 2 Diabetes**
  - Amyloid aggregation
  - Oxidative stress
  - Inflammation
  - Neural degeneration
  - Cognitive impairment

T3D-959: A PPAR delta/gamma Dual Nuclear Receptor Agonist



Ubiquitous expression

- High levels in the entorhinal cortex, hypothalamus, cerebellum, and hippocampus (dentate gyrus/CA1)
- Lower levels in the corpus callosum and caudate putamen-

PPARδ (delta)

Actions:

- Insulin sensitivity/signaling
- Fatty acid oxidation/catabolism
- Cholesterol transport
- ↑ HDL
- Reduction in adiposity, ↓ TGs
- ↓ Inflammatory signaling
- Macrophage differentiation

PPARγ (gamma)

Actions:

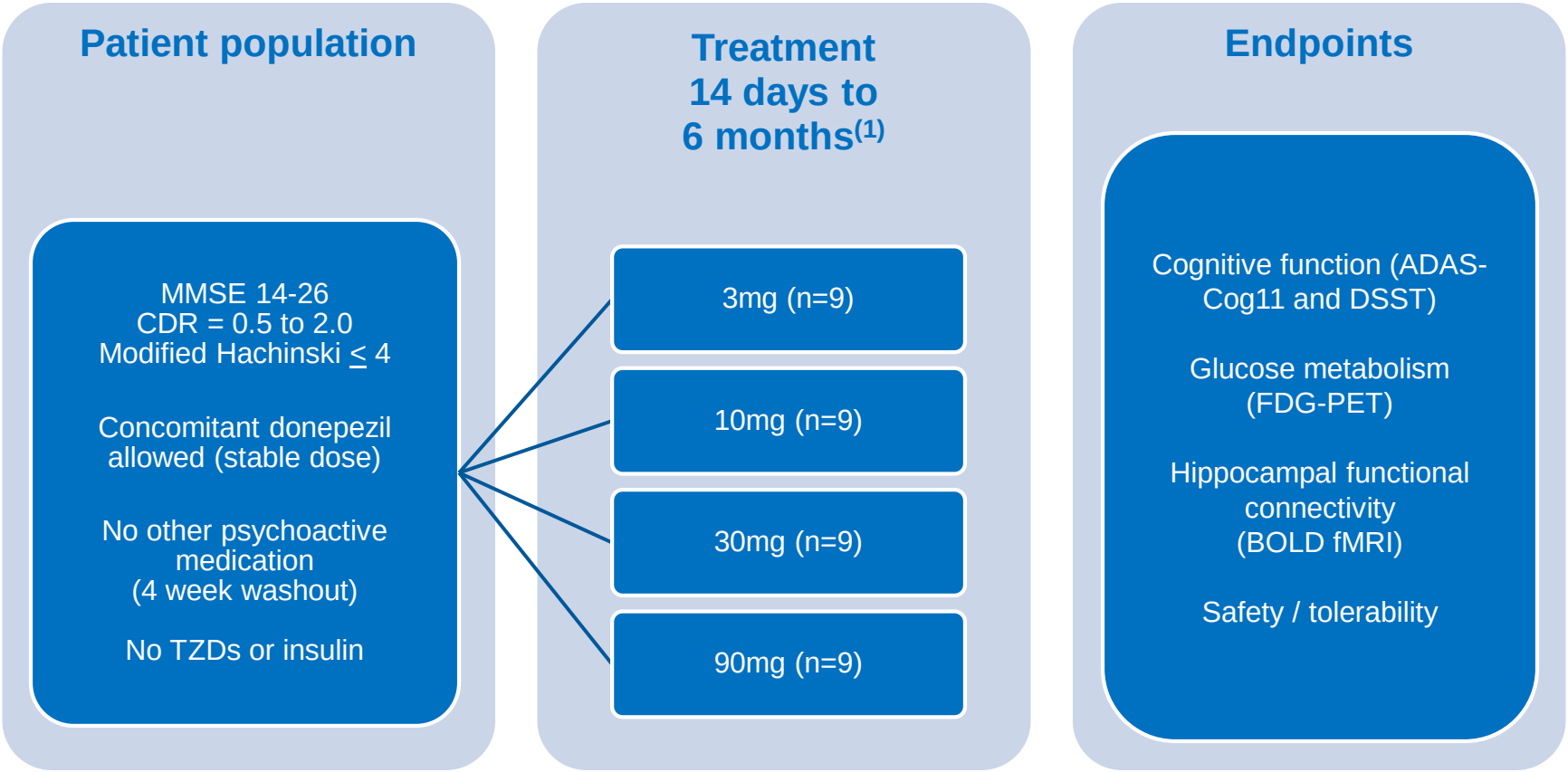
- Insulin sensitivity/signaling
- Glycogen synthesis
- Adipogenesis
- Anti-oxidation
- ↓ Inflammatory signaling
- ↑ BDNF, NGF, Klotho

Restricted Regional Expression

- Olfactory bulb
- Cortex
- Hipppocampus CA3

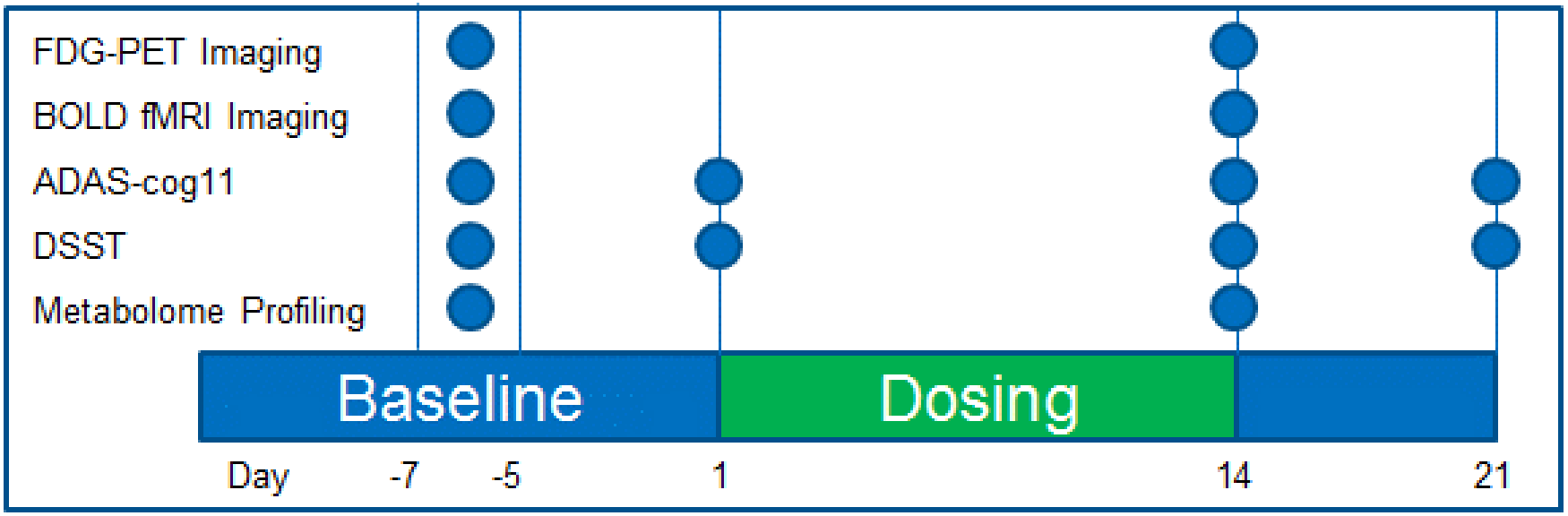
Exploratory/Feasibility Phase 2a Study of T3D-959 in Mild to Moderate Alzheimer's Disease Patients

Study Design – Main Study



(1) Original main study protocol doses patients for 14 days. FDA subsequently allowed 26-week OLE – 4 patients 15mg q.d.

Data Collection



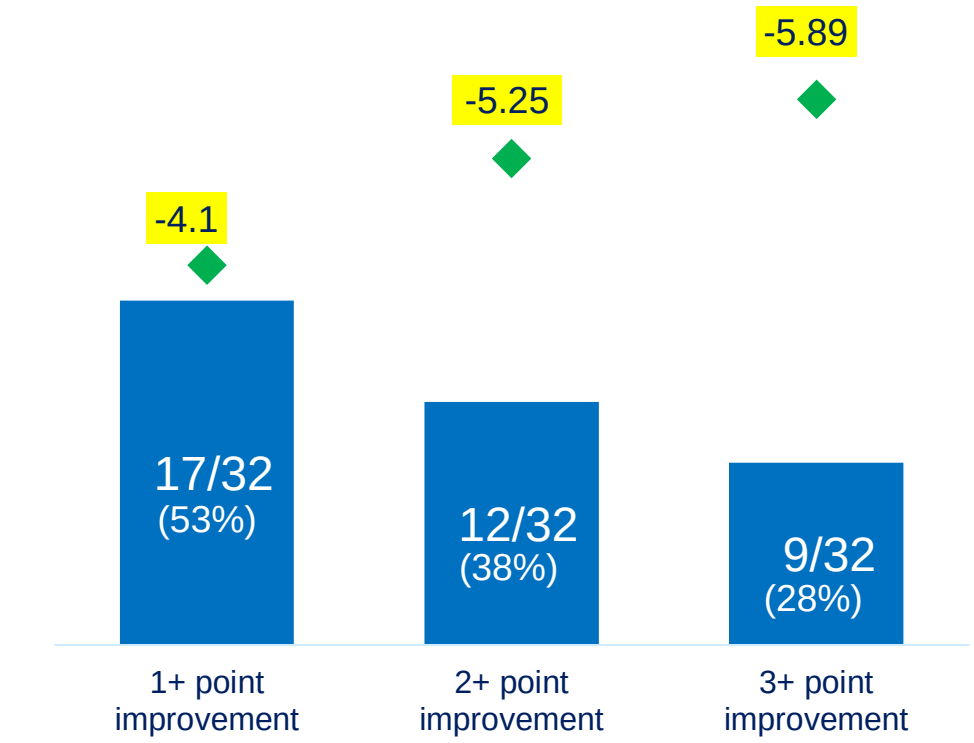
Baseline Demographics

	All patients (n=34)
MMSE	
Average (range)	19.9 (14-26)
20-26 (mild)	N=17
14-19 (moderate)	N=17
Age	
Average (range)	73.6 (57-90)
Average fasting plasma glucose	99.1mg/dL
Concurrent AD medications	N=28/34
Aricept	N=19
Namenda	N=15
Exelon	N=5
Multiple AD medications	N=14
Region of Enrollment – All U.S.	

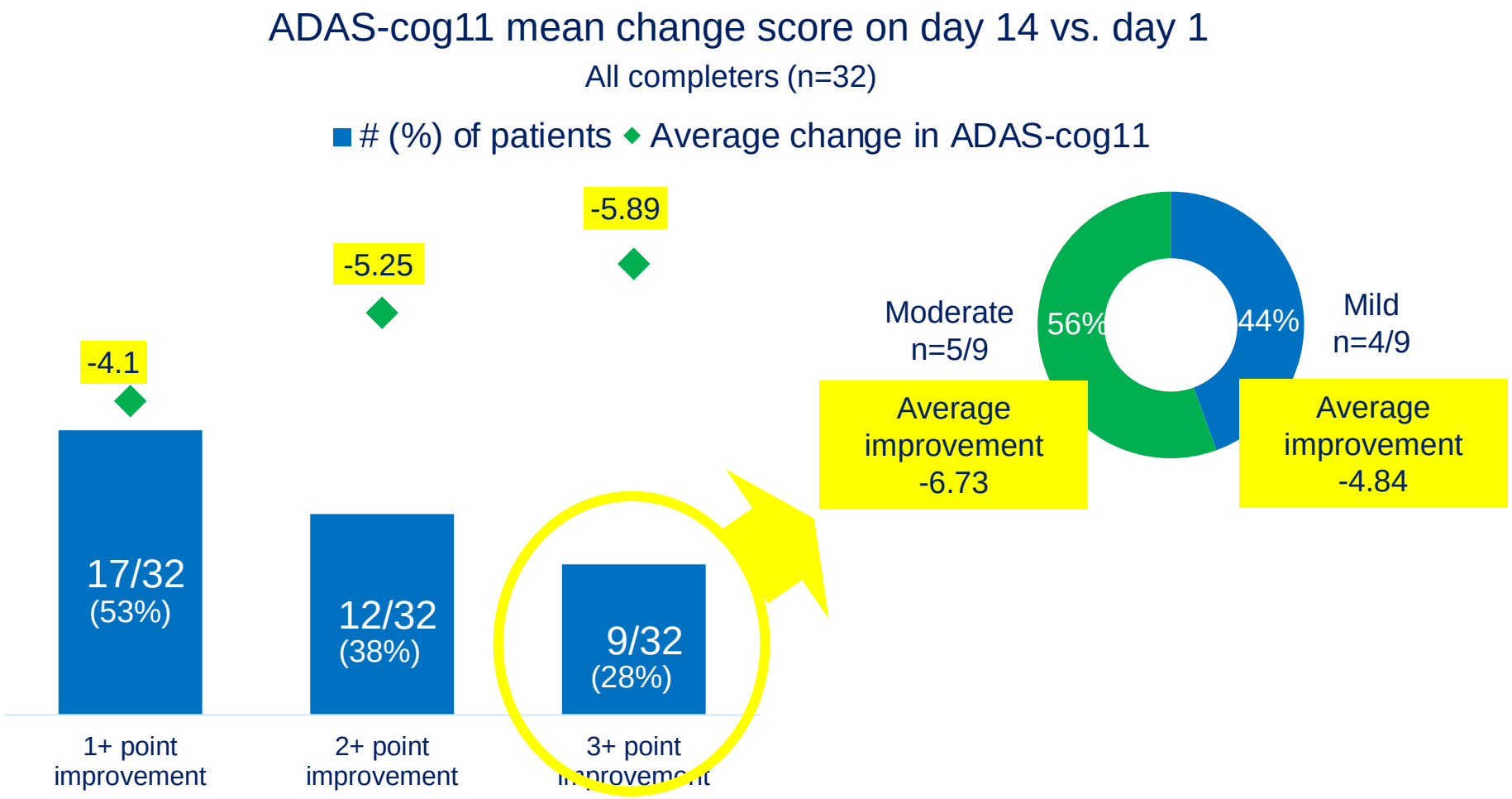
ADAS-cog11 Improvement After 14-Days Dosing

ADAS-cog11 mean change score on day 14 vs. day 1

All completers (n=32)

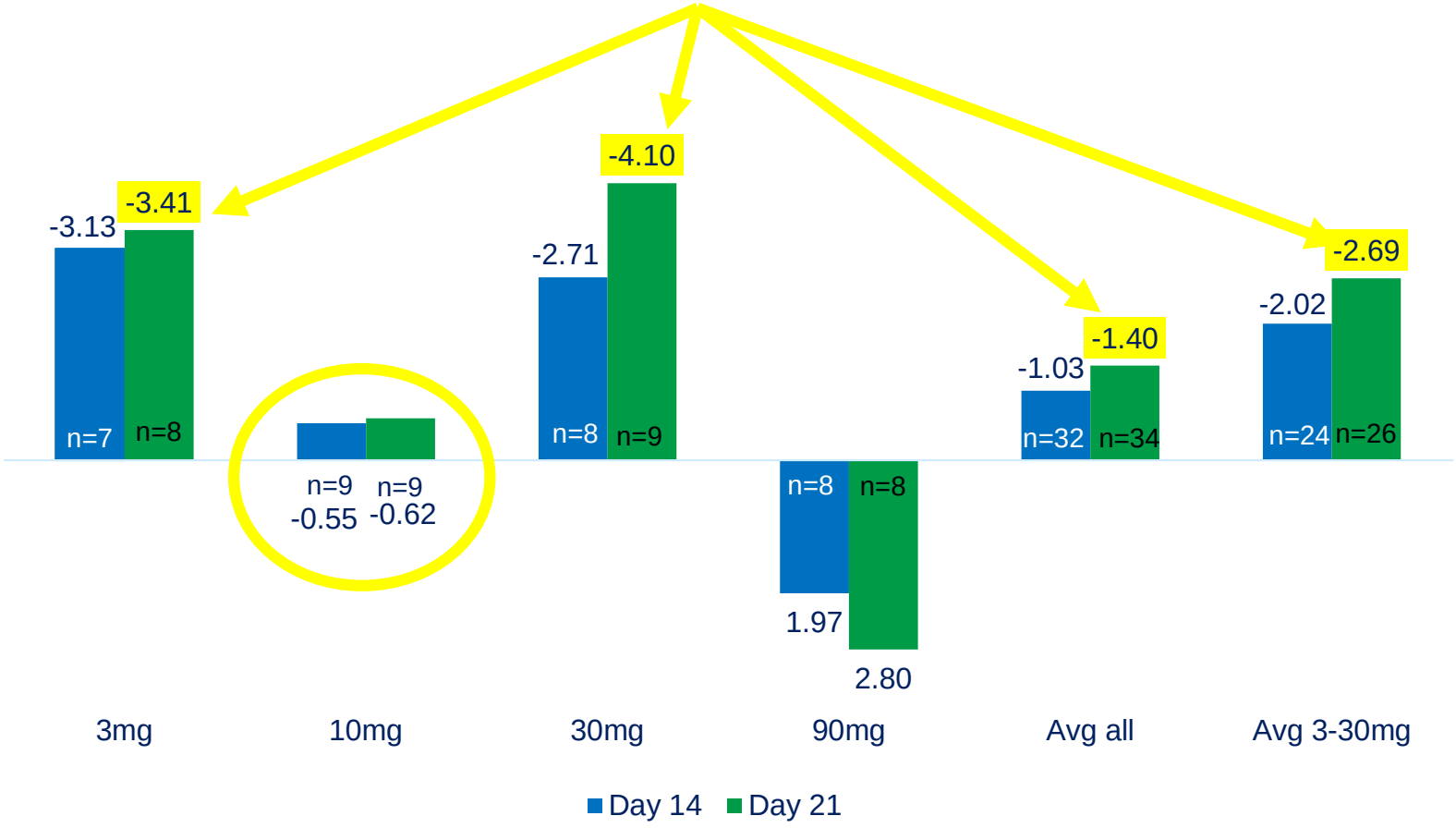


ADAS-cog11 Improvement in Both Mild and Moderate AD subjects

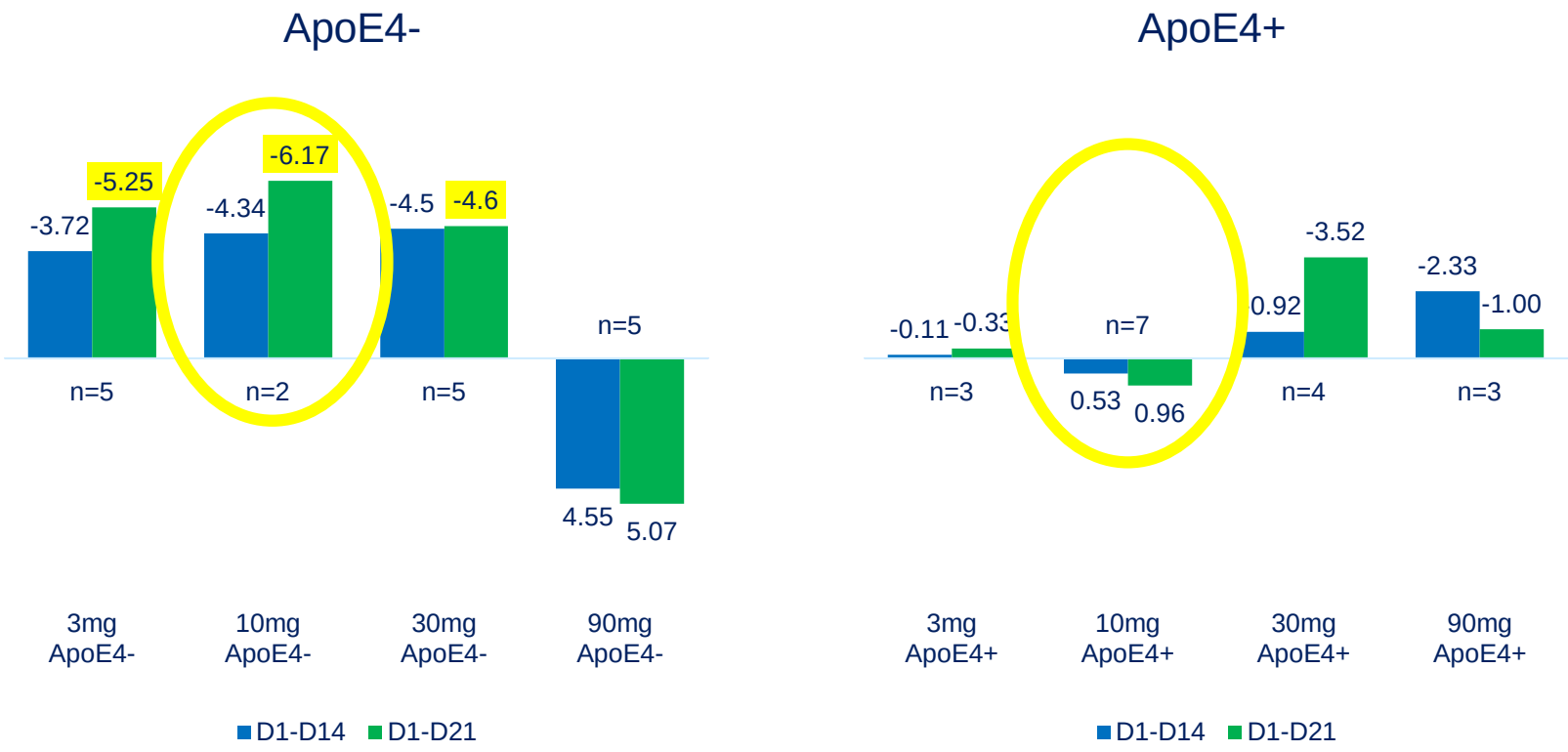


ADAS-cog11 Improvement Sustained Post-Dosing

Improvement sustained at 21 days
(7 days post discontinuation of dosing)



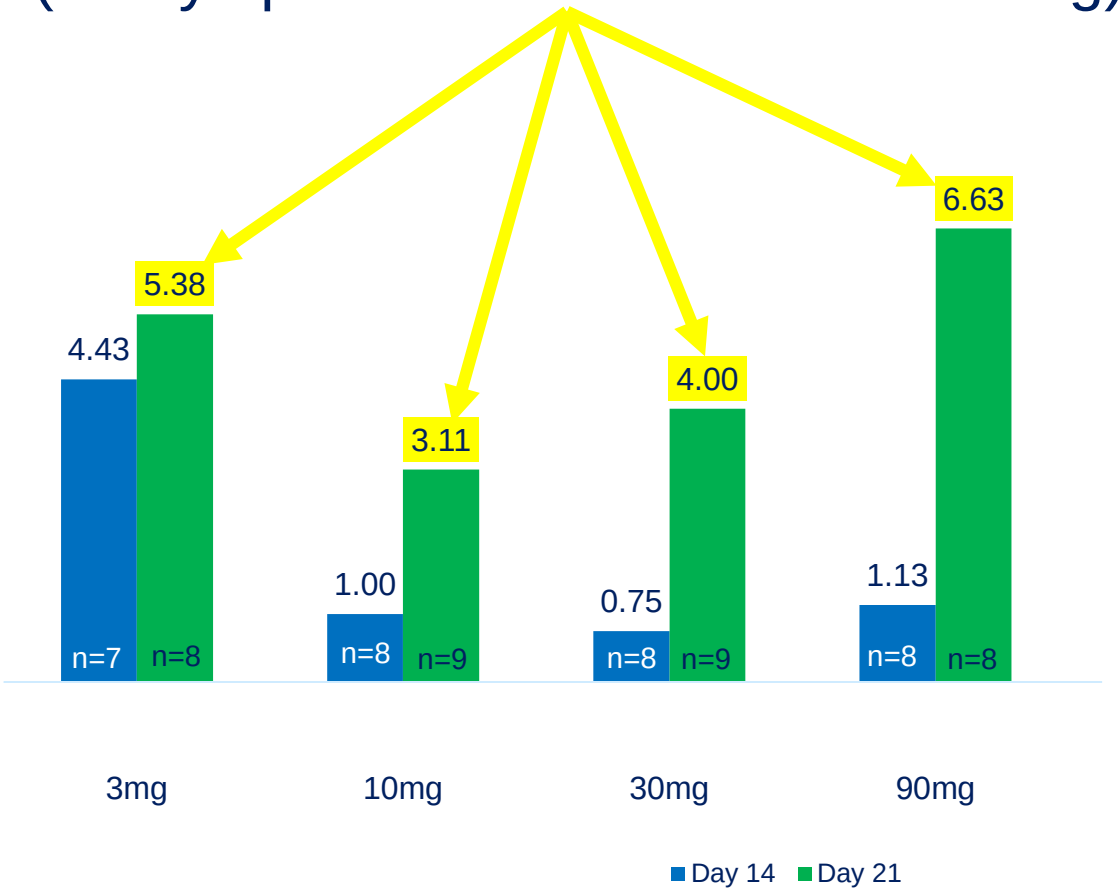
ADAS-cog11 Improvement - Dose Response Association with ApoE Genotype



Dose Trend Analysis – Significant Genotype Effect p=0.004

DSST Improvement Sustained Post-Dosing

Improvement sustained at 21 days
(7 days post discontinuation of dosing)



FDG-PET Neuroimaging

Comparisons before and after 2-weeks dosing with T3D-959

- **Static** image analyses, **not dynamic.**
- **Relative** CMRgl values calculated, **not absolute**.
  A. Regional (sROI or ROI) to Whole Brain Ratio
  B. Regional to White Matter Ratio
- Relative values **complicated by MOA** that can increase CMRgl in reference regions
- **Calculations of Relative CMRgl:**

$$\frac{\textit{End of Treatment D14}\ \text{Regional}}{\text{Whole Brain}} \xrightarrow{\text{Minus}} \frac{\textit{Baseline D0}\ \text{Regional}}{\text{Whole Brain}} = \textbf{Glucose Metabolism Ratio Change}$$

Or

$$\frac{\textit{End of Treatment D14}\ \text{Regional}}{\text{White Matter}} \xrightarrow{\text{Minus}} \frac{\textit{Baseline D0}\ \text{Regional}}{\text{White Matter}} = \textbf{Glucose Metabolism Ratio Change}$$

Pos. = Increase in Ratio
Neg. = Decrease in Ratio

FDG-PET Neuroimaging

Regional to ***Whole Brain*** Ratio: Significant CMRgl Changes

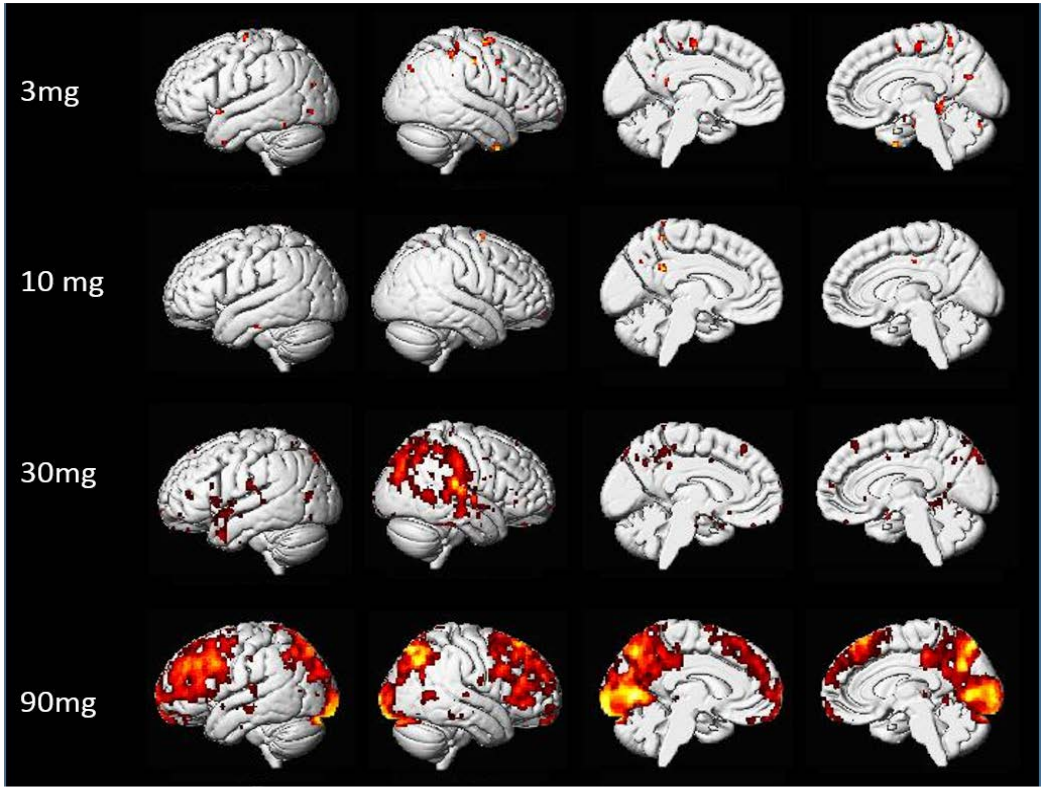
Composite of All Trial Subjects (N=34) using global brain as reference region

Conclusions:

- Brain target engagement
- Regional Specificity. Increased glucose metabolism **ratio** in brain regions critical to Alzheimer's

FDG-PET Neuroimaging

Regional to ***White Matter*** Ratio – Significant CMRgl Changes



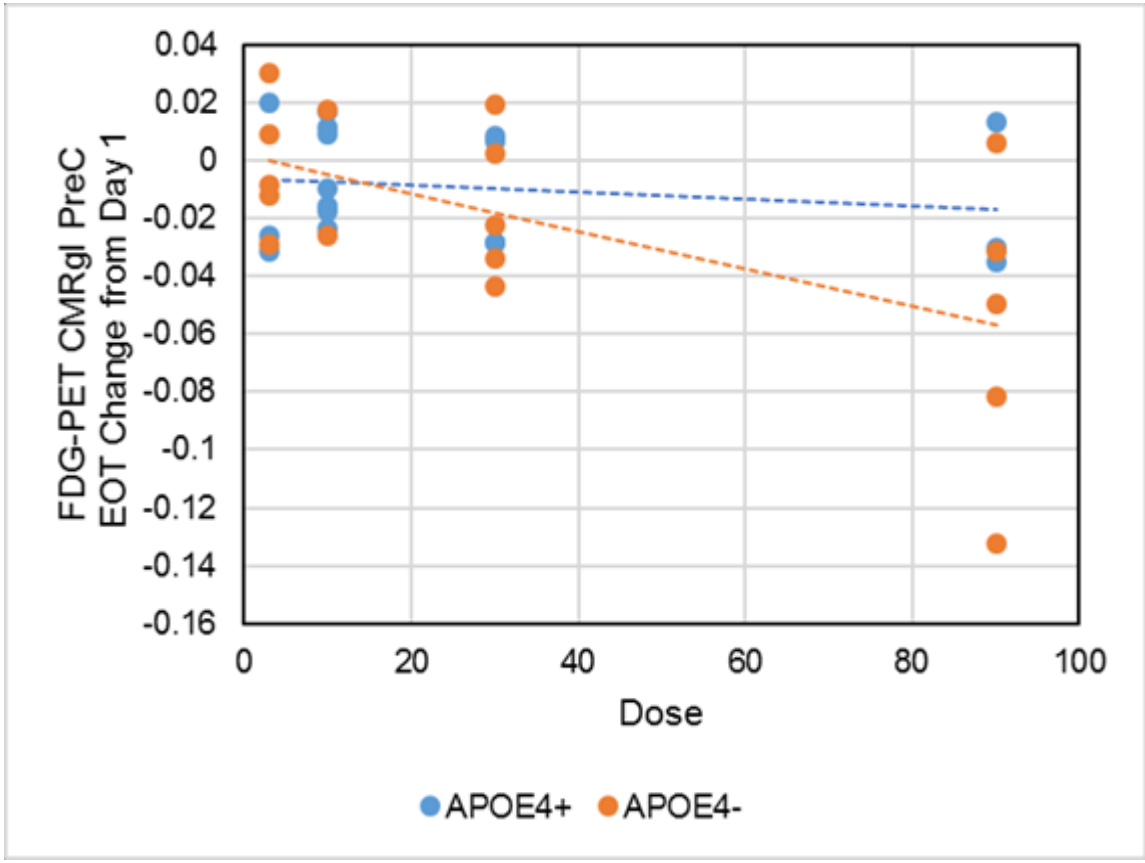
Composite of Trial Subjects by dose group (n=8-9)

Conclusions:

- Dose dependency
- Regional Specificity. Changed glucose metabolism **ratio** in AD-vulnerable regions: temporal, parietal, frontal & occipital cortices.
- Changed regional glucose metabolism **ratio** with higher doses. **Either:**
  - ↑ **White Matter CMRgl**
  - ↓ **Regional CMRgl**

Significant Change in Precuneous/White Matter Ratio by Dose

Stratified by ApoE4 Genotype



Conclusions:

- Dose / ApoE genotype – dependent decrease in relative Precuneous CMRgl

[Precuneus CMRgl may be increasing, but White Matter CMRgl may be increasing more]

Overall dose trend p-value = 0.0068

Main Study – Placebo Effect? Commentary

If there was a placebo effect then:

1. All dose groups would respond the same (The 90mg cohort does not)

2. 7-days post dosing, when patients know they are not on drug, cognitive test scores should decrease (they actually maintain or increase)

3. There would be no genotype association with cognitive test improvements (association observed)

4. No FDG-PET differences between dose arms (differences observed)

5. A difference in ADAS-cog scores between mild and moderate subjects might be expected, given moderate subjects' significantly lower propensity to exhibit 'placebo effects' (both mild and moderate subjects respond similarly)

Safety

- One drug-related AE*
  * First patient enrolled, subject 1001 (30mg) – Self-limited, resolved within 1-day
- No changes in clinical labs
- No changes in physical and neurological exams
- No changes in ECGs
- No respiratory rate or orthostatic blood pressure and heart rate changes
- No potential bone marrow effects as monitored with hematology testing
- No potential increases in plasma volume as assessed by the presence or absence of edema
- No weight gain
- No tolerability issues

Phase 2a – 26-week Open Label Extension

4 Subjects
(2 mild, 2 moderate)
All are ApoE4 Carriers
Monthly cognitive and safety assessments

At **22-weeks** dosing (15mg q.d.):

- No AEs
- No tolerability issues
- CIBIC+ improvement in all subjects Group avg. = 2.75

Data Summary

1. Rapid durable improvement (2-3 weeks) in cognition: ADAS-cog11 & DSST

2. Both mild and moderate AD subjects show equivalent response

3. Dose-dependent changes in ADAS-cog11 stratified by ApoE genotype

4. ApoE genotype as future guide of optimal dosing

5. FDG-PET results:
   - → brain penetration
   - → dose-dependent target engagement (CMRgl changes)
   - → CMRgl change / ApoE genotype association
   - → CMRgl change – regional specificity

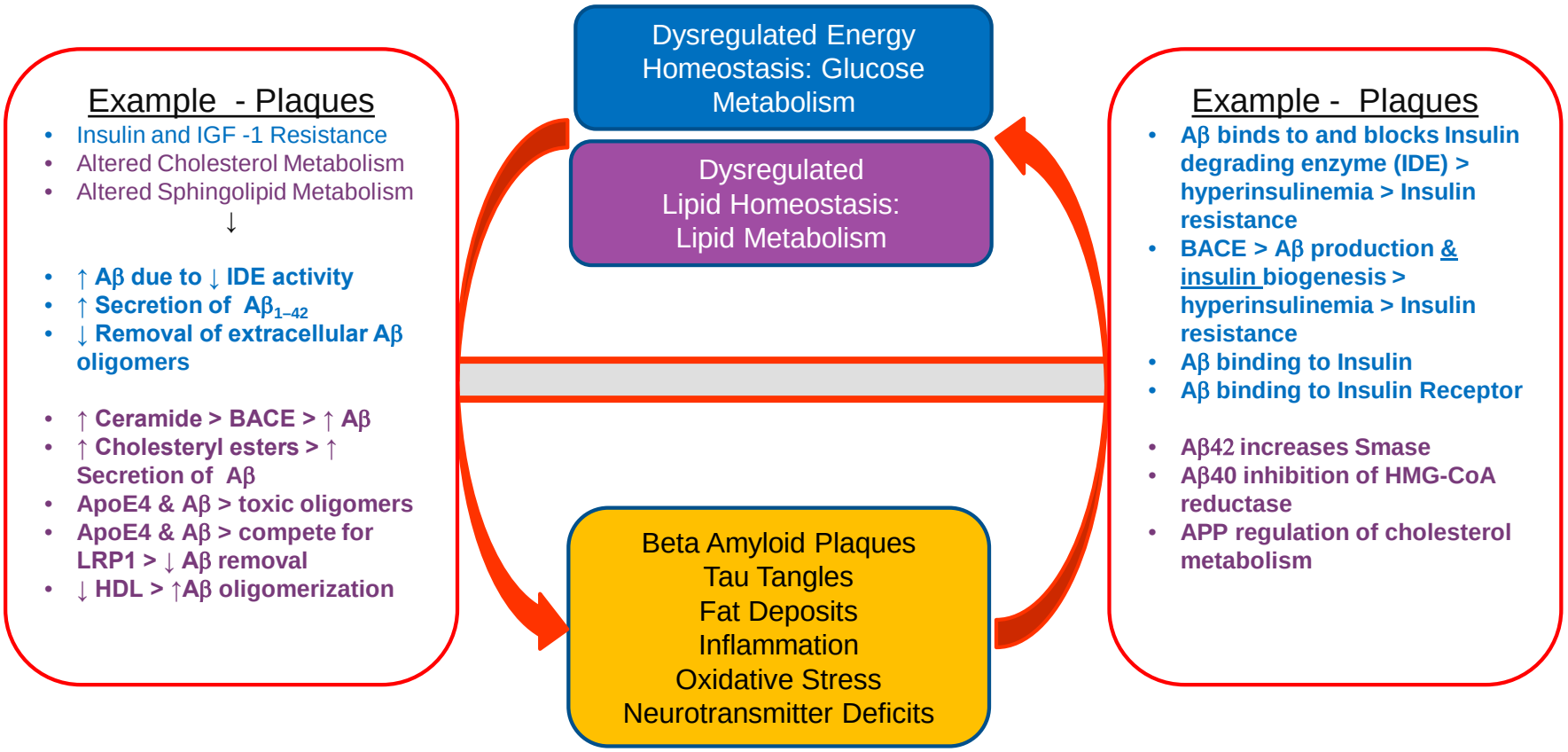
6. Short Term & Long Term Safety (in a limited number of patients)

T3D-959: Conclusions

1. Targeting AD neuro-metabolic dysfunction with T3D-959 is an attractive, and novel investigational approach
2. Results position T3D-959 as a potential disease-modifying drug therapy
3. T3D-959 will be investigated in future clinical trials as a monotherapy or combination therapy agent
4. Phase 2a study results indicate therapeutic activity in both mild and moderate severity patients
5. Results support future Phase 2b clinical testing
    A. High Safety/Tolerability √
    B. Cognitive Tests √
    C. FDG-PET √
    D. Unsolicited Caregiver Feedback √
    E. Clinical Investigator Impressions √

Appendix Slides

Metabolic Hypothesis and Plaque Hypothesis Congruence



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